

Editorial

Duration of untreated psychosis: What are we talking about?

Duration of untreated psychosis (DUP) broadly refers to the time elapsing between onset of psychosis and treatment initiation. Its relationship with outcome has been intensely studied in the framework of the development of early intervention strategies for psychosis. Results of such research are however still a matter of controversy, some studies showing a negative impact of long DUP on outcome (1–4) while others do not (5–8). In a systematic literature review, Marshall (9) nevertheless concluded that there is a significant, albeit small to moderate, negative association between DUP and outcome, and most early intervention programmes rank reduction of DUP as a primary priority.

From a clinical point of view, reduction of DUP emerges as a logical target when witnessing the collateral damage suffered by patients who experience long delays prior to onset of care (10). Additionally, recent imaging data have shown that the prodrome and the early phase of psychotic disorders are periods of active and progressive structural changes in key brain areas such as the hippocampus (11). If one assumes that there is an active process of neuroprogression underlying these changes, then the longer the DUP, the greater the time available for this potentially neurotoxic process to unfold (12). The nature of the pathogenic process remains to be fully elucidated; however, it probably includes reduction in neurotrophins, oxidative stress and inflammatory cytokines. Given the evidence that appropriate treatment is potentially neuroprotective (13), reduction in DUP could therefore be associated with reduction in potentially cumulative brain insult, and hence improvement in symptomatic and functional outcomes.

In the last few years, assessment of psychosis onset has been the object of a considerable attention, and this interest has led to both a degree of consensus about its definition and the development of scales specifically designed to determine the date of its initial occurrence (14,15). A closer look at this literature reveals on the other hand that criteria applied

to define the endpoint of DUP, in other words the time of treatment initiation, is much less consistent and vary greatly between studies.

According to international guidelines, an adequate treatment of first episode psychosis should combine adapted medication (generally utilising low-dose strategy) and psychosocial intervention delivered in the context of easily accessible and specialised treatment teams (16–18). However, despite the availability of such guidelines, the concept of ‘treatment initiation’ usually refers to the commencement of very incomplete and often ill-defined interventions (Table 1). These include ‘initiation of medication’, ‘commencement of any form of treatment’, ‘initiation of adequate treatment’, ‘time of first effective treatment’, as well as ‘hospitalisation’ or ‘entry to a specialised programme’. In addition, adherence to treatment is in the vast majority of cases not assessed when in fact clinical experience reveals that enrollment in a specialised service or prescription of medication does not necessarily equate with the person being fully engaged with the service, receiving sufficient psychosocial support, or taking medication as prescribed.

In the studies mentioned above, it is therefore highly likely that many patients for whom DUP was defined as having concluded actually remained untreated or partially treated. Only two studies defined treatment initiation on the basis of adherence to or observed response to medication treatment (14,30). However, by focusing on this aspect of treatment, they neglect the importance of psychosocial intervention in the recovery process (31), while recent randomised controlled trials have now clearly proven that integrated early intervention programmes that include specialised psychosocial treatment lead first episode psychosis patients to a better outcome than generic mental health programmes (32,33).

This lack of consistency in definition is concerning, considering that an absence of consensus on what ‘treatment initiation’ actually comprises could very well be one of the critical factors that so far

Table 1. Definitions of treatment initiation in the literature

Study	Definition applied to initiation of treatment	Limitations
Barnes et al. (19); Browne et al. (20); Craig et al. (5); Haas et al. (21); Ho and Andreasen, (7); Szymanski et al. (22); Tirupati et al. (23).	Initiation of medication	<ul style="list-style-type: none"> ● Absence of assessment of adherence to treatment ● Does not take into account psychological and case management intervention
Wiersma et al. (24)	Any form of treatment	<ul style="list-style-type: none"> ● Absence of definition of treatment
Larsen et al. (25)	Initiation of adequate treatment	<ul style="list-style-type: none"> ● Absence of definition of response
Addington et al. (26)	First effective treatment	<ul style="list-style-type: none"> ● No definition of effective treatment ● Problem with treatment resistance
Hafner et al. (27); Kalla et al. (28)	Hospitalisation	<ul style="list-style-type: none"> ● Selection bias towards patients with more acute symptoms
Carbone et al. (29); Schimmelmann et al. (4)	Entry to specialised programme	<ul style="list-style-type: none"> ● Does not mean patients are adherent to treatment
Malla et al. (30)	Medication for at least 2 months or significant response	<ul style="list-style-type: none"> ● Treatment definition restricted to medication
Singh et al. (14)	Medication with adherence (at least 75% of the dose for 75% of the time)	<ul style="list-style-type: none"> ● Treatment definition restricted to medication

limited the conclusiveness of studies exploring potential consequences of DUP. While research exploring DUP impact on outcome should not interfere with common sense arguments justifying the necessity of mental health services reforms aimed at facilitating treatment access for patients with psychosis (10), conclusive research on DUP, based on valid data, would only provide more momentum to such a reform process.

It seems therefore timely to establish a clearer definition of what should be considered as the end of the DUP period. First, given that medication is a key element in treatment of the vast majority of first episode psychosis patients, antipsychotic treatment initiation should belong to the definition. However, adherence to treatment ought to be assessed as well and the medication criterion considered fulfilled only if patients have taken their treatment for at least 75% of the time during at least 4 weeks. Second, based on the above data supporting the efficacy of specialised treatment, end of DUP should be considered only when patients are well engaged in an early intervention programme. It is clear that psychosocial treatments remain inconsistently available, and subject to the vagaries of service, economic, training and resource variables, but this is precisely what research on the impact of DUP is all about: to show that adequate treatment provided early has a positive impact on outcome of psychosis. Once this point established, the argument to justify the need for a reform of mental health programmes and for an earlier access to adequate psychosocial and medication treatment in early psychosis would only

be stronger. However, in order to supply evidence-based arguments to this debate, the definition of DUP needs to be applied with more precision.

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